SPECIFICATION

Tablet Production Method and Tablet

Technical Field

The present invention relates to a tablet production method, particularly a method wherein a tablet can be immediately disintegrated at an objective part, a method wherein a tablet with an engraved mark or a dividing line or an anomalous tablet can be produced without causing sticking and so on, and a method wherein a tablet including granule covered with film (so called multiple unit tablet) can be easily manufactured without damaging function of the granule.

The present invention also relates to a tablet which can be rapidly disintegrated at a target region of a living body such as oral cavity, a tablet wherein function of the contained granule isn't damaged, and a tablet added with function such as sustained release which isn't damaged when divided.

Background Art

A tablet and a capsule are very useful pharmaceuticals for carrying and dosing and a tablet is easy to be taken for elder person or a patient because it doesn't float on the water when dosing with water. Further, it has many advantages such that production cost can be held down. Therefore, it is a most multipurpose dosage form for oral administration and

intrabuccal administration.

In these years, a tablet which is formed anomalous other than circular in order to distinguish the product at a glance, a tablet provided with an engraved mark such as a company name or a chemical code, and a tablet with a dividing line which can be divided along the dividing line in order to administer most suitable amount of drug depending on the age and weight of a patient have been rapidly come into wide use.

There are several kinds of tablets such as an uncoated tablets made by compressing powder or granule, a coating tablet covered with a film on the tablet body for the purpose of prolongation, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste, and so on, a matrix type tablet (single unit tablet) tabletted by dispersing active substance in a base matrix of release inhibition material with hydrophobic property or hydrophilic property, and a tablet (multiple unit tablet) 101 including granule produced by tabletting molding material in which granule 102 containing active substance, diluting agent 103, and lubricant 104 are uniformly mixed liken in Fig.20(a).

As granule 102 containing active substance included in the tablet (multiple unit tablet) 101, in order that a fixed amount of active substance is continuously released for a fixed time by one dosage of the tablet 101 or the granule 102 is dissolved at an objective region such as intestine, there are granule

of which part 102a containing active substance is covered with a film 102b having sustained release or high solubility in intestine as shown in Fig.20(b) or granule wherein the active substance 102c is dispersed in a base insoluble in water such as fat, wax, and Vaseline or in the base matrix 102d of hydrophobic high molecular material such as silicon rubber, and plastic and an interface of the base matrix 102d is retreated accompanied with release of the active substance 102c from the base matrix 102d so that the active substance 102c is continuously leased as shown in Fig.20(c).

Conventionally such a tablet with an engraved mark or a dividing line, an anomalous tablet, and a tablet including granule (multiple unit tablet) has been manufactured by an internal lubricant method and an external lubricant spraying method.

According to an internal lubricant method, lubricant such as magnesium stearate, lauryl sodium sulphate, and talc are mixed in a molding material other than active substance and diluting agent in order to execute smooth tabletting by preventing adhering of molding material on punches and dies and griding between the punches and the dies at the time of producing tablets by compressing molding material by means of the punches and the dies, and for the purpose of preventing defective tablets causing sticking (phenomenon causing hurt on a tablet surface when molding material is adhered on the

punch surface), capping (phenomenon showing peeling of the top of tablet like a cap), laminating (phenomenon showing peeling of the tablet like a layer), and binding (phenomenon causing lengthwise hurt on the tablet surface when a tablet is discharged from the die).

As an external tablet spraying method, a production method has been already supposed in JP-B-41-11273 and JP-A-56-14098.

Fig.21 shows a production method disclosed in JP-B-41-11273.

According to the method comprised of charging a fixed amount of material to be tabletted in a die, tabletting the charged material in the die by means of a pair of an upper and a lower punches, and discharging the tablet, as a procedure before molding material is charged in the die 151 as shown in Fig.21(a), a spray nozzle 159 for spraying lubricant L is provided above the die 151 and lubricant L is applied on a surface 153s (lower surface) of the upper punch 153 and a surface 154s (upper surface) of the lower punch 154, both of which are provided for the die 151 which comes to a place where the spray nozzle 159 is placed. Then molding material is charged in the die 151 as shown in Fig.21(b), and the charged material m is compressed by means of the upper punch 153 on which lower surface 153s is applied with lubricant L and the lower punch 154 of which upper surface 154s is applied with lubricant as shown in Fig.21(c).

The member indicated by the numeral 152 in Fig.21 shows

a rotary table provided with the die 151 (The same numeral is used in Fig.22.).

Fig.22 shows a tablet production method described in JP-A-56-14098.

According to this method, before molding material is charged in a die 151, a spray 156 for spraying lubricant L and a nozzle 159 for spraying air are provided above the die 151. Lubricant L is sprayed in the spray 156 when the die 151 comes where the spray 156 is provided as shown in Fig.22(a), lubricant is applied on a surface 154s (upper surface) of a lower punch 154 provided for the die 151 as shown in Fig.22(b). As shown in Fig.22(c), compressed air is sprayed on the lower punch 154 at a position where the nozzle 159 is provided, lubricant L applied on the upper surface 154s of the lower punch 154 is blown upwardly to be dispersed, then the dispersed lubricant L is attached on an inner wall 151s of the die 151 and a surface 153s (lower surface) of an upper punch 153. Thereafter, molding material m is compressed to produce a tablet by means of lubricated inner wall 151s of the die 151, lubricated lower surface 153s of the upper punch 153, and lubricated upper surface 154s of the lower punch 154.

However, a tablet produced by an internal lubricant method includes lubricant therein and has a problem wherein disintegrating time of a tablet is delayed because of water repellency of lubricant so that it becomes hard to produce a

tablet which is required to be rapidly disintegrated at a target region like an intrabuccally rapidly disintegrable tablet.

Moreover, when a tablet with an engraved mark, a tablet with a dividing line or an anomalous tablet with different shape are produced according to prior internal lubricant method or external lubricant spraying method, the produced tablet is apt to cause sticking, capping, laminating and binding.

According to an internal lubricant method, high tabletting pressure is required (generally 1 ton/cm^2 - 2 ton/cm^2) in order to obtain practical hardness. Therefore, when a tablet containing granule (multiple unit tablet) 101 is produced according to this method, the film 102b formed on the surface of the granule 102 contained in the tablet 101 is damaged when tabletted, or the granule 102 is plastically deformed or destroyed when unreasonable force is applied to the granule 102 so that functions of the granule 102 contained in the tablet 101 such as rapid release, sustained release, prolongation of mode of action, or function of dissolving at an objective region can't be obtained.

Conventionally as a method to prevent the film 102b formed on the surface of the granule 102 from being damaged while tabletting, there has been disclosed multiple granule in JP-A-62-103012, a chewable drug tablet containing gustation shielding agent in JP-A-2-106, and a rapid release microcapsule in JP-A-57-150612. However, they are produced by

pharmaceutically devising the construction and material of the film 102b. According to such a method, material and construction to be selected are limited and a film usually used for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, and prevention of bitter taste can't be used.

Further, as a method to keep the function of the film by restraining breakage of the film of granule, there is a method wherein practical hardness of a tablet is obtained by tabletting while dispersing granule in a large amount of diluting agent. According to such a method, there is a problem that a tablet containing a large amount of granule therein can't be produced.

From the above-mentioned problems, application of a tablet containing granule (multiple unit tablet) is limited and pharmaceuticals containing granule, so called microcapsule are not launched on the marked as a formulation such as tablet which is easily taken by a patient or patients but as formulations such as capsule or granule which are not easily taken by a patient or patients.

A single unit type tablet which is coated with such as film or sugar on the surface of the tabletted uncoated tablet is popular as a tablet having the functions such as prolongation of made of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine or

prevention of bitter taste. However, in case that such a single unit type tablet is formed as a dividable tablet having a dividing line on the surface, the film is destroyed and the function added to the tablet is lost when the tablet is divided. Therefore, it can't meet the requirement of physician or pharmacist of a hospital or a clinic to launch on the market a dividable tablet with prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine or prevention of bitter taste which can minutely prepare an appropriate amount in conformity to each patient.

The present invention is proposed to solve the above-mentioned problems. The first object of the present invention is to provide a production method of a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet.

The second object of the present invention is to provide a production method of a tablet with an engraved mark or a dividing line or an anomalous tablet without causing sticking, capping, laminating and binding.

The third object of the present invention is to provide a tablet production method wherein a tablet containing granule (multiple unit tablet) can be produced without damaging the function of the granule (which may be called as a microcapsule) contained therein, to provide a tablet containing granule (multiple unit tablet) which can be immediately dissolved at

an objective region, a tablet containing granule (multiple unit tablet) of which function isn't damaged without specially devising the construction and the material of the film formed on the granule. Moreover, the object of the present invention is to provide a dividable tablet with a dividing line which has prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste, and such functions aren't damaged when the tablet is divided.

Disclosure of the Invention

The inventors of the present invention have done research on a tablet production method for a long time and found by experiments that when punches and a die of a tabletting machine are housed in a spraying chamber, pulsating vibration air is generated in the spraying chamber, lubricant is applied on the surfaces of the punches and the die, and molding material is tabletted by means of the lubricated punches and die to produce a tablet with an engraved mark or a dividing line or an anomalous tablet, such tablets haven't caused sticking, capping, laminating and binding. After hard endeavor, they have completed the present invention.

Further the inventors have already proposed a tablet production method in JP-A-7-124231 wherein molding material is prevented from adhering on the punches and the dies so that

molding material can be continuously tabletted smoothly and stably for a long time and moreover a tablet can be produced without adhering molding material on the punches and the dies even if the amount of used lubricant is remarkably reduced. The inventors have thought that when this method is used, a tablet which has enough practical hardness and further its disintegrant time isn't delayed can be produced even if tabletting pressure is low. After hard endeavor, they have completed the present invention.

According to the tablet production method as set forth in claim 1, a tablet including at least active substance is produced by means of a die and a pair of punches. The method is comprised of preparing molding material including active substance; housing the pair of punches and the die in a spraying chamber; generating pulsating vibration air and spraying lubricant mixed in air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the die housed in the spraying chamber while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air, and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

Several kinds of lubricant can be used for the tablet production method of the present invention. Lubricant isn't specifically limited, for example, there are stearate acid metal salt (magnesium stearate, calcium stearate and so on), stearic

acid, sodium lauryl sulfate, sodium lauryl magnesium, powdered gum arabic, carnauba wax, anhydrous silicic acid, magnesium oxide, silic acid hydrate, boric acid, fatty acid sodium salt, leucine, and so on which have been commonly used. One of them may be used solely or more than two of them may be combined.

According to the tablet production method of the present invention, diluting agent is added in molding material for forming the shape of a tablet other than active substance.

As for diluting agent, there are several kinds, such as saccharides (lactose, sucrose, glucose, mannitol, and so on), starch (for example, potato, wheat, corn and so on), inorganic substance (calcium carbonate, calcium sulfate, sodium bicarbonate, sodium chloride, and so on), crystalline cellulose, powdered plant (powdered glycyrrhiza, powdered gentian, and so on).

Molding material containing active substance may include binder, supplement such as solution adjuvant, solubilizer, or disintegrant, corrigent, colorant, adjuvant for pharmaceiticals, antioxidant, preservative, opacifying agent, antistatic agent, aroma, sweetening agent, fluidizing agent, flavoring agent, and so on if required other than active substance and diluting agent. However, molding material is powdered or granular material which doesn't include lubricant.

"Pulsating vibration air" in the present invention means a wave of air of which air pressure is changed. Positive or

negative pulsating vibration air may be used and of which amplitude, wave length, wave shape, frequency, and period may not be limited if it can generate air vibration all over the spraying chamber and forcibly diffuse the particle of lubricant sprayed therein.

"Positive pulsating vibration air" used in this invention includes both positive pulsating vibration air of which peak and valley are positive and positive pulsating vibration air of which peak is higher than atmospheric pressure and valley is almost the same as atmospheric pressure.

"Negative pulsating vibration air" used in this invention includes both pulsating vibration air of which peak and valley are negative and pulsating vibration air of which peak is almost the same as atmospheric pressure and valley is negative.

Conditions of pulsating vibration air depend on size and shape of punches and dies of a tabletting machine, size and shape of a spraying chamber, how a lubricant spraying means is provided, and description of active substance. Therefore, conditions can't be simply defined, however it is easily defined based on experiments.

According to this tablet production method, pulsating vibration air is generated and lubricant is sprayed in the spraying chamber. As a result, the sprayed lubricant is mixed with pulsating vibration air.

Further according to this method, lubricant is applied on

the surfaces of the die and the pair of punches under a condition wherein lubricant is mixed with pulsating vibration air, namely a condition wherein lubricant is hardly attached on the surfaces of the punches and the die.

When lubricant is designed to be applied on the surfaces of the punches and the die under such a hard condition, lubricant can be uniformly applied thereon. This fact has been confirmed by an experiment by the present inventors.

Consequently, molding material is prevented from adhering on the pair of punches and the die while tabletted so that sticking is hardly caused.

Moreover, as the result that lubricant is uniformly applied on the surface of the pair of punches and the die, the produced tablet doesn't cause sticking even if the amount of used lubricant per a tablet is remarkably reduced comparing with the prior internal lubricant method and the prior external lubricant spraying method.

Therefore, a tablet of which surface a minute amount of lubricant is attached can be produced. Such a tablet doesn't happen that disintegrant time doesn't delay because of water repellency of lubricant.

According to the production method, a tablet which can be rapidly disintegrated at an object region such as target region of living body can be produced.

Further according to the production method, because

lubricant isn't included in molding material, a tablet with practical hardness can be produced even if tabletting pressure is lower than that of prior art when molding material is tabletted by means of a pair of punches and a die.

Hence, when a tablet including granule having film on the surface is produced, the film isn't destroyed.

Also when a tablet including granule containing active substance in a base matrix is produced, the function of the contained matrix isn't damaged.

According to the tablet production method as set forth in claim 2, a tablet including at least active substance is produced by means of a die and a pair of punches. The method is comprised of the steps of; preparing molding material including active substance; housing the pair of punches and the dies in a spraying chamber; spraying lubricant mixed in pulsating vibration air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the die housed in the spraying chamber; and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

According to this tablet production method, lubricant mixed with pulsating vibration air is designed to be sprayed in the spraying chamber.

Further according to this method, lubricant is applied on the surfaces of the die and the pair of punches under a condition wherein lubricant is mixed with pulsating vibration air, namely

a condition wherein lubricant is hardly attached on the surfaces of the punches and the die.

When lubricant is designed to be applied on the surfaces of the punches and the die under such a hard condition, lubricant can be uniformly applied thereon.

Consequently, molding material is prevented from adhering on the pair of punches and the die while tabletted so that sticking is hardly caused.

Moreover, as the result that lubricant is uniformly applied on the surfaces of the pair of punches and the die, the produced tablet doesn't cause sticking even if the amount of used lubricant per a tablet is remarkably reduced comparing with the prior internal lubricant method and the prior external lubricant spraying method.

Therefore, a tablet of which surface a minute amount of lubricant is attached can be produced. Such a tablet doesn't happen that disintegrant time delays because of water repellency of lubricant.

According to the production method, a tablet which can be rapidly disintegrated at an object region such as target region of living body can be produced.

Further according to the production method, because lubricant isn't included in molding material, a tablet with practical hardness can be produced even if tabletting pressure is lower than that of prior art when molding material is tabletted

by means of a pair of punches and a die.

Hence, when a tablet including filmed granule on the surface is produced, the film isn't destroyed.

Also when a tablet including granule containing active substance in a base matrix is produced, the function of the contained matrix isn't damaged.

The tablet production method as set forth in claim 3 is characterized in that pulsating vibration air used in the method of claim 2 is positive pulsating vibration air.

According to this method, a spraying means for spraying lubricant mixed with positive pulsating vibration air is required to be provided so that the system can be simplified.

Further the inventors have paid attention in JP-A-7-124231 that when material is tabletted at a remarkably low pressure, the produced tablet has enough practical hardness. They have thought that a tablet including granule can be produced by this method without damaging the coated film of the granule, so called microcapsule, damaging the contained granule, nor deforming plasticity. After hard endeavor, they have completed the present invention.

According to the tablet production method as set forth in claim 4, a tablet including granule containing at least active substance is produced by means of a die and a pair of punches. The method is comprised of the steps of; mixing granule containing active substance and diluting agent uniformly and preparing

molding material including granule containing active substance; housing the pair of punches and the dies in a spraying chamber; generating pulsating vibration air and spraying lubricant mixed in air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the dies housed in the spraying chamber while the lubricant sprayed in the spraying chamber is mixed with the pulsating vibration air; and tabletting the molding material including granule containing the active substance by means of the pair of punches and the die on which surfaces the lubricant is applied.

"A tablet including granule containing at least active compound" includes a tablet produced by tabletting only granule containing active substance and a tablet produced by tabletting molding material in which granule containing at least active substance, diluent, bulking agent, filler, and other diluting agent such as excipient are uniformly mixed. Further molding material may include supplement such as solution adjuvant, solubilizer, and disintegrant, antioxidant, preservative, opacifying agent, antistatic agent, aroma, sweetening agent, fluidizing agent, flavoring agent, colorant and so on.

"Granule including active substance" includes granule which is provided with film on the part including at least active substance (therapeutic main ingredient) for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine,

prevention of bitter taste, and granule in which active substance is dispersed in a base matrix.

Coating material for the film covering the surface of the part including active substance (therapeutic main ingredient) isn't required to be special. It may be generally used film coating agent such as sugar coating, ethylcellulose (EC), hydroxypropylsellulose (HPC), hydroxypropylmethylcellulose phthalate (HPMC), carboxymethylcellulose, and cellulose group such as hydroxypropylmethylcellulose, acetate succinate (HPMCAS), carboxymethylethylcellulose (CMEC), and cellulose acetate phthalate (CAP), acrylic acid group such as methaacrylic acid copolymer, enteric coating agent such as natural product like shellac, sustained release coating agent such as ethylcellulose (EC), sucrose ester, aminoalkylmetaacrilate copolymer, copolymer of ethylacrylate - methylmethacrylate, and several kinds of material such as coating material disclosed in JP-A-57-150612, JP-A-62-103012, and JP-A-2-106.

According to this method, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film provided for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter

taste and the base matrix aren't devised.

The production method of a tablet including granule containing at least active substance by means of a die and a pair of punches as set forth in claim 5 is comprised of the steps of; mixing granule containing active substance and diluting agent uniformly and preparing molding material including granule containing active substance; housing the pair of punches and the die in a spraying chamber; spraying lubricant mixed in pulsating vibration air in the spraying chamber; applying lubricant on the surfaces of the pair of punches and the die housed in the spraying chamber; and tabletting the molding material including granule containing the active substance by means of the pair of punches and the die on which surfaces the lubricant is applied.

According to this method, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film provided for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste and the base matrix aren't devised.

The tablet production method as set forth in claim 6 is characterized in that the pulsating vibration air used in the

tablet production method in claim 5 is a positive pulsating vibration air.

According to this method, a spraying means for spraying lubricant mixed with positive pulsating vibration air is required to be provided so that the system can be simplified.

The tablet production method as set forth in claim 7 proposes a preferable embodiment of granule containing active substance (so called microcapsule) to be included in molding material and defies granule containing active substance described in any one of claims 4 - 6 is granule containing active substance and diluting agent.

According to this method, granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule) so that the particle diameter and particle size of the granule containing active substance can be easily changed by the diluting agent.

Therefore, a tablet can be easily produced by controlling the diameter and the size of granule containing active substance so as to facilitate coating a film on the surface.

Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

The tablet production method as set forth in claim 8 proposes another preferable embodiment of granule containing active substance (so called microcapsule) to be included in molding

material and defies granule containing active substance used in the method as set forth in any one of claims 4 - 6 is granule containing active substance in base matrix.

"Granule containing active substance in base matrix" means granule wherein active substance (powder) is uniformly dispersed in a base insoluble in water such as fat, wax, and Vaseline or in a base matrix of hydrophobic high molecular material such as silicon rubber, and plastic.

According to this production method, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the function of base matrix even if granule contained in the tablet includes active substance in the base matrix.

The tablet production method as set forth in claim 9 proposes further preferable embodiment of granule containing active substance (so called microcapsule) to be included in molding material and defies granule containing active substance used in the method as set forth in any one of claims 4 - 8 is granule of which part containing active substance is coated with film.

According to this production method, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the coating film even if granule contained in the tablet is coated with a film.

A coating method such as well known fluidized bed coating may be used as a method for coating granule with a film.

According to the tablet production method as set forth in claim 10, the following steps as set forth in claim 1 or 4 are continuously executed; housing the pair of punches and the die in the spraying chamber; generating pulsating vibration air, spraying lubricant mixed in air in the spraying chamber; and applying the lubricant on the surfaces of the pair of punches and the die while the lubricant sprayed in the spraying chamber is mixed with pulsating vibration air; and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

According to this method, tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the die so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

The tablet production method as set forth in claim 11 is characterized in that the following steps in claim 2 or 5 are continuously executed; housing the pair of punches and the die in the spraying chamber; spraying lubricant mixed in positive pulsating vibration air in the spraying chamber, and applying the lubricant on the surfaces of the pair of punches and the die; and tabletting the molding material by means of the pair of punches and the die on which surfaces the lubricant is applied.

According to this method, tabletting is continuously

executed utilizing the fact that molding material isn't adhered on the punches and the die so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

The tablet production method as set forth in claim 12 is characterized in that in the method of any one of claims 1 - 11 punches and a die construct a female mold of a tablet having an engraved mark or a dividing line and an anomalous tablet.

"Anomalous tablet" in this specification means a tablet with a shape except for round, for example, track (capsule), rugby ball, polygon such as triangle, rectangle, pentagon, and so on, diamond, almond, bombshell, half moon, heart, star, and so on.

According to this method, because lubricant is applied on the surface of the punches and the die constructing a female mold for a tablet with an engraved mark or a dividing line and for an anomalous tablet in the spraying chamber in which pulsating vibration air is generated, lubricant can be applied uniformly comparing with the prior external lubricant spraying method. As a result, molding material is hardly attached on the surface of the punches and the die while compressing a tablet with an engraved mark or a dividing line or an anomalous tablet so that sticking, capping, and laminating of such a tablet are prevented.

The tablet production method as set forth in claim 13 is

characterized in that in the production method in any one of claims 1 - 12 tabletting pressure of the step for tabletting the molding material by means of the lubricated pair of punches and die is low.

"Low pressure" in this specification means that tabletting pressure is lower comparing with the prior internal lubricant method and the prior external lubricant spraying method. More concretely explained, this tablet production method can produce a tablet having enough practical level hardness even if its tabletting pressure is less than or equal to 1 ton/cm^2.

According to this tablet production method, as tabletting pressure for compressing molding material is low, tabletting can be executed without destroying a film even if granule contained in the tablet is covered with a film. Further, if granule contained in a tablet includes active substance in a base matrix, tabletting can be executed without destroying the function of the base matrix.

The tablet production method as set forth in claim 14 is characterized in that in the production method in any one of claims 1 - 13 the amount of lubricant sprayed in the spraying chamber is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

It is preferable to reduce the amount of lubricant as far as possible in order to prevent extension of disintegration time of a tablet and lowering of hardness. It is preferable

to set the amount of lubricant used for a tablet to be compressed is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

Depending on an experiment, it was found that a tablet didn't cause tabletting problems such as sticking and could be produced continuously even if the amount of lubricant was greater than 0.0001 weight percent and less than or equal to 0.1 weight percent per a tablet.

According to this method, lubricant is applied on the surface (inner wall) of the die, the surface (lower surface) of the upper punch, and the surface (upper surface) of the lower punch, all of which are housed in the spraying chamber, by means of pulsating vibration air. Namely lubricant is applied on the surfaces under a condition where lubricant is hardly attached on the surfaces. Therefore, a minute amount of lubricant can be applied on the surface (inner wall) of the die, the surface (lower surface) of the upper punch, and the surface (upper surface) of the lower punch. As a result, even if the amount of lubricant sprayed in the spraying chamber is only minute despite of kinds of active substance, diluting agent and lubricant, molding material can be prevented from sticking on the punches and the die of the tabletting machine. Consequently the amount of lubricant sprayed for tabletting at one time can be remarkably reduced.

In accordance with this method, the produced tablet doesn't

include lubricant therein and minute amount of lubricant is attached on the surface so that disintegration time isn't delayed.

Therefore, if the tablet produced by this method is used as an uncoated, it becomes rapidly disintegrable tablet and a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet can be easily produced. Further if a film coat which can be dissolved at an objective region is executed on the surface of a tablet, the tablet itself is immediately dissolved at a desired region when a film coat is dissolved, so that a tablet which can be dissolved at an objective region can be produced.

Further according to this method, tablet can be produced at a low tabletting pressure. When a tablet including granule containing active substance is produced, the granule is hardly damaged or plastic deformation is hardly caused when tabletting. Therefore, the function of the granule containing active substance in the tablet isn't apt to be damaged.

Therefore, according to the production method, if the produced tablet including granule containing active substance is used as an uncoated tablet, it becomes rapidly disintegrable tablet and a tablet which is required to be immediately disintegrated at an objective region and the granule containing active substance can be dissolved while showing its function like an intrabuccally rapidly disintegrable tablet can be easily

produced. Further if a film coat which can be dissolved at an objective region is executed on the surface of a tablet, the tablet which is required that it is immediately dissolved at a desired region when a film coat is dissolved can be produced.

The tablet as set forth in claim 15 is provided with lubricant only on the surface of a tablet including granule containing active substance in diluting agent and the amount of lubricant is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

It is preferable to reduce the amount of lubricant as far as possible in order to prevent extension of disintegration time of a tablet and lowering of hardness. It is preferable to set the amount of lubricant used for a tablet to be compressed is greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet.

Depending on an experiment, it was found that a tablet didn't cause tabletting problems such as sticking and could be produced continuously even if the amount of lubricant was greater than or equal to 0.0001 weight percent and less than or equal to 0.1 weight percent per a tablet.

According to the tablet, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

Therefore, if the tablet is used as an uncoated tablet,

it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and active substance contained in the tablet is immediately released.

Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at the objective region when the film coat is dissolved, so that active substance contained in the tablet is immediately released.

The tablet as set forth in claim 16 has lubricant only on the surface of the tablet including granule containing active substance in diluting agent.

According to the tablet, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and granule containing active substance (so called microcapsule) included in the tablet is immediately released.

Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at the objective region when

the film coat is dissolved, so that granule containing active substance (so called microcapsule) included in the tablet is immediately released.

The tablet as set forth in claim 17 - 19 defines preferable construction of the granule containing active substance of the tablet as set forth in claim 16.

According to the tablet as set forth in claim 17, the tablet as set forth in claim 16 is characterized in that the granule containing active substance is granule containing active substance and diluting agent.

According to such a tablet, as granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule), the particle diameter and size of the granule can be easily modified by diluting agent.

Therefore, a tablet production can be easily executed by controlling the particle diameter and size of the granule so as to be easily coated with a film on the surface of the tablet.

Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

According to the tablet as set forth in claim 18, the tablet in claim 16 is characterized in that the granule containing active substance is granule including active substance in base matrix.

According to such a tablet, as diluting agent used as bulking

agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

Further, as the tablet includes granule containing active substance in the base matrix, the base matrix can achieve its desired objective function.

For example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of sustained release by the base matrix.

Therefore, if unfilmed granule containing active substance and granule containing active substance in base matrix are mixed in a tablet, they are immediately released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

As for the granule containing active substance in the base matrix, for example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of prolongation of mode of action by the base matrix.

Namely, the tablet yields both rapid onset of action and prolongation of mode of action.

If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and granule containing such agent in the base matrix are mixed.

Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

The tablet as set forth in claim 19 is characterized in that the granule containing active substance of the tablet of any one of claims 16 - 18 is granule of which part containing active substance is covered with film.

According to such a tablet, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

Further, as the tablet includes granule containing active substance, a film coated on the surface of the granule containing active substance brings out a desired objective function.

For example, the film coated on the granule containing active substance aims at prolongation of mode of action, the tablet also yields prolongation of mode of action because of the film.

Therefore, if unfilmed granule containing active substance and filmed granule containing active substance are mixed in a tablet, they are released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset

of action.

As for the filmed granule containing active substance, for example, if the film aims at prolongation of mode of action, the tablet also becomes to have prolongation of mode of action because of the function of the film. Namely, the tablet has both rapid onset of action and prolongation of mode of action.

If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and filmed granule containing such agent are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

According to the tablet as set forth in claim 20, the amount of lubricant used in the tablet described in any one of claims 16 - 19 is greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight percent per a tablet.

It is preferable to reduce the amount of lubricant as far as possible, preferably greater than or equal to 0.0001 weight percent and less than or equal to 0.1 weight percent per a tablet.

Because the tablet is provided with a minute amount of lubricant on the surface, its disintegration time doesn't delay.

According to the tablet as set forth in claim 21, the tablet described in any one of claims 15 - 20 is provided with a dividing

line on the surface thereof.

Because the tablet has a dividing line, it can be easily divided along the line. Therefore, appropriate amount of drug depending on the weight or age of a patient can be taken by a patient.

The tablet as set forth in claim 22 is characterized in that the shape of the tablet described in any one of claims 15 - 21 is anomalous.

Because the tablet has anomalous shape, drugs can be easily distinguished by its shape. Therefore, medication error is hardly happened.

The tablet as set forth in claim 23 is characterized in that the standard deviation of disintegration time of the tablet or elution time of the active substance described any one of claims 15 - 22 is less than or equal to 15 percent of average disintegrating time or average elution time.

The fact that the standard deviation of disintegration time of the tablet or elution time of the active substance can be less than or equal to 15 percent of average disintegrating time or average elution time is an effect of the experiment done by the present inventors.

Further according to the experiment done by the present inventors, it was found that the standard deviation of disintegration time of the tablet or elution time of the active substance could be less than or equal to 10.0 percent of average

disintegrating time of the tablet or average elution time fo the active substance. Further it was also found that the standard deviation of disintegrating time of the tablet or elution time of the active substance could be less than or equal to 7.5 percent of average disintegrating time or average elution time, further less than or equal to 7.0 percent.

Because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance. Therefore, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 15.0 percent of average disintegrating time or average elution time can be easily produced.

Further, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 10.0 percent of average disintegrating time or average elution time, which has been considered to be difficult in the prior art, can be easily produced.

Moreover, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than or equal to 7.5 percent, further 7.0 percent, of average disintegrating time or average elution time, which has been impossible to produce in the prior art as far

as the inventors know, can be produced.

Because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance.

Hence, there is no variation of the time before appearing the effect of drugs between tablets.

The tablet as set forth in claim 24 is characterized in that the lubricant of the tablet described in any one of claims 15 - 23 is magnesium stearate.

When magnesium stearate is used as lubricant, the amount of lubricant contained in the tablet can be easily measured by atomic absorption spectrometry.

Brief Description of Drawings

Fig.1 shows a schematic construction of an enlarged view around a rotary table of a rotary type tabletting machine used for executing the present invention.

Fig.2 shows a schematic section of the enlarged view around the rotary table of the rotary type tabletting machine shown in Fig.1.

Fig.3 is a schematic view around a spraying chamber, Fig.3(a) schematically shows a construction of the spraying chamber, and Fig.3(b) schematically shows a construction of a pulsating vibration air generation means.

Fig.4 explains a concrete example of pulsating vibration air, Fig.4(a) and Fig.4(b) show negative pulsating vibration air respectively.

Fig.5 is a schematic view around a spraying chamber, Fig.5(a) schematically shows a construction of the spraying chamber, and Fig.5(b) schematically shows a construction of a pulsating vibration air generation means.

Fig.6 explains a concrete example of pulsating vibration air, Fig.6(a) and Fig.6(b) show positive pulsating vibration air respectively.

Fig.7 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.8 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.9 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.10 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.11 schematically explains many kinds of tablets produced in experiments. A schematic plane view of each tablet is shown at left and its schematic side view is shown at right.

Fig.12 is a graph showing cross relationship between tabletting pressure and hardness of produced tablet.

Fig.13 is a graph showing cross relationship between time and dissolution rate.

Fig.14 is a graph showing cross relationship between time and dissolution rate.

Fig.15 schematically shows a sectional view of means (metering feeder) for quantitatively supplying lubricant contained in a hopper into a conduit.

Fig.16 is a schematic plane view showing one embodiment of an elastic membrane used for the means (metering feeder) in Fig.15.

Fig.17 schematically shows operations of the means (metering feeder) shown in Fig.15.

Fig.18 is a schematic plane view showing another embodiment of an elastic membrane used for the means (metering feeder) in Fig.15.

Fig.19 is a schematic sectional view showing another embodiment of pulsating vibration air generation means.

Fig.20 schematically explains a construction of a tablet, Fig.20(a) explains a multiple unit type tablet, Fig.20(b) and Fig.20(c) explain the construction of the granule included in the multiple unit type tablet.

Fig.21 schematically shows the tablet production method described in JP-B-41-11273.

Fig.22 schematically shows the tablet production method described in JP-A-56-14098.

Disclosure of the Invention

The present invention will be detailed hereinafter referring to the attached drawings.

(Embodiment of the Invention 1)

In this embodiment the production method of a tablet which is immediately disintegrated at an objective region will be explained referring to the attached drawings.

Here the present invention will be explained by an example using a rotary type tabletting machine.

Fig.1 shows schematic construction by enlarging one part around a rotary table of a rotary type tabletting machine used for executing the present invention.

Fig.2 is a schematic section when one part of Fig.1 around the rotary table is enlarged.

As shown in Fig.1 and Fig.2, the rotary type tabletting machine A is comprised of a rotatably provided rotary table 2 having plural dies 1, ··· in circumferential direction, plural upper punches 3, ··· and plural lower punches 4, ··· provided so as to correspond to each dies 1, ···. A spraying chamber 8 is provided at P1 which is before a point P2 where molding material is charged in the die 1. A pulsating vibration air generation means 7 is connected to the spraying chamber 8 and a spray nozzle

9 for spraying lubricant L is provided in the spraying chamber 8. In this embodiment, an air source 10 such as a cylinder charging compressed air is connected to the spray nozzle 9 and lubricant L is designed to be sprayed from the spray nozzle 9 by the air generated from the source 10.

Next, tablet production procedure using this machine A will be explained.

The rotary table 2 is rotated at a fixed speed, pulsating vibration air is generated in the spraying chamber 8 by driving the pulsating vibration air generation means 7 when the die 1 comes to the point P1 where the spraying chamber 8 is provided according to rotation of the rotary table 2, lubricant L is simultaneously sprayed from the spray nozzle 9, and lubricant L is applied on a surface (inner wall) 1s of the die 1, a surface (lower surface) 3s of the upper punch 3, and a surface (upper surface) 4s of the lower punch 4.

Then, molding material m is charged in the die 1 which comes to the point P2 for charging molding material m in the die 1 accompanied with rotation of the rotary table 2 and extra molding material m is scraped. Thereafter, when the die 1 charged with molding material m comes to a point P3 for compressing molding material m, molding material m in the die 1 is compressed to produce a tablet by means of the upper punch 3 of which surface (lower surface) 3s is applied with lubricant L and the lower punch 4 of which surface (upper surface) 4s is applied with

lubricant L. Further, when the die 1 comes to a point P4, a tablet T is discharged from the die 1 so that the tablet T is produced.

Fig.3(a) shows schematic construction around the spraying chamber 8 and Fig.3(b) illustrates construction by an example of pulsating vibration air generation means 7.

In this example, the pulsating vibration air generation means 7 is connected to the spraying chamber 8 via a conduit 13.

In Fig.3(b) the numeral 71 shows a blower, 72 shows a cylindrical tube, 73 shows a valve element provided rotatably around a rotary axis 74 so as to divide inside of the tube 72 into two parts. The conduit 13 and a conduit 14 coupled to the blower 71 are connected at a given place of the side of the tube 72. The valve element 73 is designed to be rotated at a desired rotational velocity by means of a valve rotation control means (not shown).

When the blower 71 is rotated at a given rotation number and the valve element 73 is also rotated at a given rotational speed, the spraying chamber 8 and the blower 71 are connected as the valve element 73 is positioned at a place shown by a solid line in the figure. When the valve element 73 is positioned at a place shown by a dotted line, the spraying chamber 8 and the blower 71 are blocked off by the valve element 73. Accordingly, pulsating vibration air with its peak at

atmospheric pressure and its valley at negative pressure shown in Fig. 4(a) or pulsating vibration air with its peak and valley at negative pressure shown in Fig.4(b) can be produced in the spraying chamber 8.

Here "negative pressure" means that the pressure in the spraying chamber 8 is lower than outside pressure (atmospheric pressure).

When lubricant L is sprayed from the spray nozzle 9 while generating pulsating vibration air shown in Fig.4(a) or Fig.4(b), sprayed lubricant L is diffused by the pulsating vibration air and is uniformly applied on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3 and the surface (upper surface) 4s of the lower punch 4 both of which are provided so as to correspond to the die 1 housed in the spraying chamber 8.

According to this tablet production method, as lubricant L can be uniformly applied on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (upper surface) 4s of the lower punch 4, molding material m can be prevented from adhering on the die 1, the upper punch 3, and the lower punch 4 of the tabletting machine A even if the amount of lubricant L sprayed in the spraying chamber 8 is only a little regardless of the kinds of active substance, diluting agent, and lubricant.

This method is characterized in that the amount of lubricant

sprayed in the spraying chamber is remarkably reduced utilizing this effect. The spray amount of lubricant L to be sprayed in the spraying chamber 8 is controlled to be greater than or equal to 0.0001 weight % and less than or equal to 0.2 weight % per the weight of tablet. Further it may be controlled greater than or equal to 0.0001 weight % and less than or equal to 0.1 weight %.

According to this method, only a part of lubricant L applied on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (upper surface) 4s of the lower punch 4 exists on the surface of the tablet and the tablet doesn't include lubricant L therein. Therefore, the used amount of lubricant L for the tablet T is remarkably small comparing with the tablet produced by the prior production method. Hence, a problem, which has been found in the prior tablet, wherein disintegration time of tablet delays because of water repellency of lubricant L is never happened.

Further, because lubricant L isn't included in the molding material m, produced tablet can obtain practical hardness even if tabletting pressure is low (practically less than 1 ton/c m^2) comparing with the case that molding material m including lubricant L is tabletted.

Accordingly, if the tablet T produced by the production method is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and is suitable as a tablet which is required

to be disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet.

If a film coat which can be dissolved at an objective region is executed on the surface of the tablet T, the tablet itself can be immediately dissolved at the objective region so that a tablet which can be dissolved at an objective region can be produced.

Further, when granule of which surface of a part containing active substance is filmed is included in a tablet as granule containing active substance, the film coated on the surface isn't destroyed at the time of compression (tabletting) because the tablet T can be compressed (tabletted) at low pressure. Accordingly, the film coated on the granule containing active substance can bring out a desired objective function.

For example, the film coated on the granule containing active substance aims at prolongation of mode of action, the tablet also has sustained release because of the film.

Therefore, if unfilmed granule containing active substance and filmed granule containing active substance are mixed in the tablet T, they are immediately released from the tablet T when the tablet T is disintegrated. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

As for the filmed granule containing active substance, for

example, if the film aims at prolongation of mode of action, the tablet also becomes to have prolongation of mode of action because of the function of the film.

Namely, the tablet has both rapid onset of action and prolongation of mode of action.

If the active substance is analgesic (morphine hydrochloride and so on), anti-inflammatory agent (indometacin, diclofenac sodium and so on), or antidote(sulphyrine and so on), unfilmed granule containing such agent and filmed granule containing such agent are mixed in the tablet T. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long and also has rapid onset of action when a patient takes this medicine can be obtained.

Moreover, when granule containing active substance in a base matrix is included in the tablet T as granule containing active substance, the function of the base matrix isn't destroyed at the time of compression (tabletting) because the tablet T can be compressed (tabletted) at low pressure. Accordingly, the base matrix can bring out a desired objective function.

Therefore, if unfilmed granule containing active substance and granule containing active substance in the base matrix are mixed in the tablet T, they are immediately released from the tablet T when the tablet T is disintegrated. The active

substance contained in the unfilmed granule is immediately absorbed in a body when the tablet T is disintegrated. Therefore, the tablet has superior rapid onset of action.

As for the granule containing active substance in the base matrix, for example, if the base matrix aims at prolongation of mode of action, the tablet T also becomes to have prolongation of mode of action because of the function of the base matrix.

Namely, the tablet T has both rapid onset of action and prolongation of mode of action.

If the active substance is analgesic (morphine hydrochloride and so on), anti-inflammatory agent (indometacin, diclofenac sodium and so on), or antidote(sulphyrine and so on), unfilmed granule containing such agent and granule containing such agent in the base matrix are mixed in the tablet T. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long and also has rapid onset of action when a patient takes this medicine can be obtained.

It is preferable to reduce the amount of lubricant L sprayed in the spraying chamber 8 as far as sticking of molding material m to the die 1, the upper punch 3, and the lower punch 4 of the tabletting machine A is prevented. In order to prevent that the disintegration time of the produced tablet is extended

and the hardness is lowered, it is preferably greater than or equal to 0.0001 weight percent and less than or equal to 0.2 weight percent per a tablet, although it depends on the nature of the molding material. According to an experiment, when the amount of lubricant L was greater than or equal to 0.001 weight percent and less than or equal to 0.1 weight percent per a tablet, it was found that problems such as sticking weren't caused and continuous tabletting could be executed.

Because lubricant L is uniformly applied on the surface of the tablet T (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance.

Hence, there is no variation of the time before appearing the effect of drugs between tablets.

Next, the present invention will be explained based on concrete experimental data.

(Experiment 1)

According to normal fluid-bed granulation method, polyvinyl alcohol was sprayed on the powder of which prescription was shown in the following table 1, particle was grown, and granulated material with prescribed size was manufactured. Then, the obtained granule was sized by means of a No.28 mesh. Next, it was tabletted to produce a 130mg tablet at a speed of rotating a rotary table 2 at 30 times per a minute by means of the tabletting machine A with 7mm diameter punch and die

set.

When tabletting, magnesium stearate was used as lubricant. The amount of air sprayed from the nozzle 9 shown in Fig.3(a), rotation number and suction amount of the pulsating vibration air generation means 7 were controlled in such a manner that the amount of the magnesium stearate sprayed in the spraying chamber 8 was adjusted such that weight % of lubricant L included in one produced tablet became 0.03 weight % for the entire amount of the tablet.

More concretely, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter lower than atmospheric pressure was used in this experiment.

WSG-type 15 by Glatt Co., Ltd. was used as a fluid-bed granulator and HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of a tabletting machine.

Table 1

combined ingredient	weight %
Levodopa (Japanese Pharmacopoeia)	9.0
Lactose	57.5
Cornstarch	28.5
Polyvinyl alcohol	5.0
Total	100.0

(Comparison 1)

Magnesium stearate was added as lubricant for the granule produced like the experiment 1 in a ratio of 0.03 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by an internal lubricant method at a speed of rotating the rotary table at 30 times per minute by means of a set of 7mm punch and die so as to produce the material into a 130mg tablet. However, tablet wasn't continuously produced because molding material adhered on the punches and the dies.

Then in order to solve this, magnesium stearate was added as lubricant for the granule used in the experiment 1 in a ratio of 0.8 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by an internal lubricant method at a speed of rotating the rotary table at 30 times per minute by means of a set of

7mm punch and die so as to produce the material into a 130mg tablet.

However, it was hard to continuously produce a tablet because molding material adhered on the punches and the dies.

HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as the tabletting machine A.

(Comparison 2)

The granule produced like the experiment 1 was tabletted by means of a set of 7mm punch and die so as to produce a 130mg tablet. Stearate magnesium was applied on the surfaces 3s, 4s of the punches 3, 4 and the surface 1s of the die 1 according to the method described in JP-B-41-11273 so that the weight % of lubricant became 0.03 weight % per a produced tablet. Then the material was continuously tabletted at a speed of rotating the rotary table at 30 times per minute.

HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as the tabletting machine A.

Next, disintegration test according to Japanese Pharmacopoeia was executed for three kinds of tablets produced according to the experiment 1, the comparison 1, and the comparison 2 at a given test number (N=5).

The result is shown in Table 2.

Table 2

	Tabletting Pressure (ton/cm²)	hardness (kg)	Disintegration time (min) (n = 5) Average measurement (standard variation)
experiment 1	0.7	9	6.0 (±0.2)
comparison 1	0.7	6	10.2 (±0.9)
comparison 2	0.7	9	8.0 (±0.6)

According to the table 2, it was found that the experiment 1 had high hardness comparing with the comparison 1 and had short disintegration time comparing with the comparisons 1 and 2. And also its disintegration time doesn't widely vary.

Also it was found that in the experiment 1 had the same hardness as the comparison 2, however, disintegration time was

short and variation of disintegration time was small.

When the rotary type tabletting machine A provided with the pulsating vibration air generation means 7 shown in Fig.1 was used, it was found that the produced tablet has practical hardness at a tabletting pressure of 0.7 ton/cm^2.

As the result, it was also found that in the experiment 1 lubricant was uniformly applied on the surface of the tablet.

The standard deviation of the disintegration time of the tablet in the experiment 1 was 0.2 and the disintegration time of each tablet was less than or equal to 7%. From the above experiment, it was found that the standard deviation of the disintegration time of the tablet or the diluting time of active substance could easily become less than or equal to 15% of the average disintegration time of the tablet or the average diluting time of active substance.

Moreover according to the above experiment, it was found that the standard deviation of the disintegration time of the tablet or the diluting time of active substance could easily become less than or equal to 10% of the average disintegration time of the tablet or the average diluting time of active substance. Furthermore, it was also found that the standard deviation of the disintegration time of the tablet or the diluting time of active substance could easily become less than or equal to 7.0% of the average disintegration time of the tablet or the average diluting time of active substance.

Therefore, it was cleared that a tablet without having variation of disintegration time and diluting time of active substance could be easily produced.

In this embodiment, the system shown in Fig.3(b) was used as a pulsating vibration air generation means 7. However, it is only an example and any kinds of system can be used as the pulsating vibration air generation means 7. For example, the blower 71 may be connected to the end of the conduit 13, a solenoid valve may be provided in the middle of the conduit 13 for opening and closing the conduit 13, the blower 71 may be rotated at a given rotation number so as to suck air in the spraying chamber 8, and the conduit 13 may be opened or closed at a prescribed period by the solenoid valve. Otherwise the blower 71 may be connected to the end of the conduit 13, the blower 71 may be rotated fast or slowly at a given period, and air in the spraying chamber 8 may be sucked strongly and weakly.

Also in the above-mentioned embodiment, the pulsating vibration air shown in Fig.4(a) or Fig.4(b) was generated. The system shown in Fig.5 may be constructed and the pulsating vibration air shown in Fig.6(a) or Fig.6(b) may be generated in the spraying chamber 8. Namely, in the embodiment shown in Fig.5, a pulsating vibration air generation means 7A is connected to the end of the conduit 13, a hopper 15 storing lubricant L is connected in midstream of the conduit 13, and a compressed air generation means 16 such as a cylinder charging

compressed air is connected to the hopper 15 as shown in Fig.5(a). The numeral 17 in Fig. 5(a) shows a blower provided if required. When the blower 17 is driven, air in the spraying chamber 8 is sucked and pulsating vibration air supplied in the spraying chamber 8 and lubricant L are induced to be discharged from the spraying chamber 8.

The system shown in Fig.5 is provided with the nozzle means for spraying lubricant mixed with positive pulsating vibration air so that the construction of the spraying chamber 8 can be simplified.

As shown in Fig.5(b), the pulsating vibration air generation means 7A is provided with the blower 71, the cylindrical tube 72 connected to the conduit 13 between the blower 71 and the hopper 15, and the valve element 73 which is rotatable around the rotary axis 74 in the tube 72 and is designed to divide the inside of the tube 72 into two parts. The conduit 13 and the conduit 14 coupled to the blower 71 are connected to the side of the tube 72. The valve element 73 is constructed so as to be rotated at a desired rotational velocity by means of a valve rotation control means (not shown).

When the blower 71 is rotated at a given rotation number to send air to the spraying chamber 8 and the valve element 73 is also rotated at a given rotational velocity, the spraying chamber 8 and the blower 71 are connected when the valve element 73 is located at the place shown as a slid line in the figure.

When the valve element 73 is located at a dotted line, the spraying chamber 8 and the blower 71 are blocked off by the valve element 73. Accordingly pulsating vibration air with its peak at positive pressure and its valley at atmospheric pressure as shown in Fig.6(a) is generated in the spraying chamber 8. Otherwise, pulsating vibration air with its peak and valley at positive pressure as shown in Fig.6(b) may be generated in the spraying chamber 8. While keeping this condition, the compressed air generation means 16 may be driven to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L may be supplied in the spraying chamber 8 together with the current of pulsating vibration air.

Here positive pressure means that the pressure in the spraying chamber 8 is higher than the pressure outside of the spraying chamber 8.

Otherwise, the blower 71 may be provided at the end of the conduit 13, the solenoid valve for opening and closing the conduit 13 may be provided in the midstream of the conduit 13, the blower 71 may be rotated at a given rotation number to feed air in the spraying chamber 8, the conduit 13 may be opened and closed periodically by the solenoid valve, then pulsating vibration air may be generated in the spraying chamber 8 and the conduit 13. While keeping such a condition, the compression air generation means 16 may be driven to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant

L is supplied in the spraying chamber 8 together with the current of pulsating vibration air. On the other hand, the blower 71 may be connected at the end of the conduit 13, the blower 71 may be rotated fast or slowly at a given period so as to feed air strongly or weekly in the spraying chamber 8, and pulsating vibration air may be generated in the spraying chamber 8 and the conduit 13. While keeping this condition, the compression air generation means 16 may be driven so as to feed lubricant L contained in the hopper 15 to the conduit 13 and a fixed amount of lubricant L may be supplied in the spraying chamber 8 together with the current of pulsating vibration air.

When pulsating vibration air shown in Fig.6(a) or Fig.6(b) is used wherein its period is more than or equal to 1Hz and less than or equal to 10Hz, its peak is about 10% - 5% higher than atmospheric pressure, and its valley is almost equal to or a litter higher than atmospheric pressure, the effect same as the experiment 1 can be obtained (same as following embodiment 2 and 3).

(Embodiment of the Invention 2)

Here, an example of producing several shapes of tablets by means of punches and a die for constructing a female mold of a tablet with an engraved mark or a dividing line, or an anomalous tablet as the die 1, the upper punch 3, and the lower punch 4 of the rotary type tabletting machine A.

(Experiment 2)

Several anomalous tablets having the shape shown in Fig.7 - 11 were produced using a female mold for constructing a tablet shown in Fig. 7 - Fig.11 as the die 1, the upper punch 3, and the lower punch 4 of the rotary type tabletting machine A.

More concretely explained, according to normal fluid-bed granulation method, glybuzole and mannitol were mixed at a ratio of 7 : 3, polyvinyl alcohol was sprayed, granule having a prescribed particle size and prescribed particle size distribution was manufactured, and the obtained granule was sized by means of a No.28 mesh.

The punches 3, 4 and the die 1 for constructing a female mold of the tablets shown in Fig.7 - Fig.11 were housed in the spraying chamber 8, pulsating vibration air shown in Fig.4(a) was generated, magnesium stearate was applied as lubricant L on the surface 3s, 4s of the punches 3, 4 and the surface 1s of the die 1, and granule was continuously tabletted at a speed of rotating the rotary table 1 at 30 times per a minute by means of the lubricated punches 3, 4 and the die 1.

When tabletting, magnesium stearate was used as lubricant. The amount of air sprayed from the nozzle 9 shown in Fig.3(a), rotation number and suction amount of the pulsating vibration air generation means 7 were controlled in such a manner that the amount of the magnesium stearate sprayed in the spraying chamber 8 was adjusted such that weight % of lubricant L included in one produced tablet became 0.03 weight % for the entire amount

of the tablet.

More concretely, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter higher than atmospheric pressure was used in this experiment.

WSG-type 15 by Glatt Co., Ltd. was used as a fluid-bed granulator and HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of a tabletting machine.

The tablet in Fig.7(a) shows a circular tablet generally called flat plain, the tablet in Fig.7(b) shows a circular tablet generally called shallow concave plain, the tablet in Fig.7(c) shows a circular tablet generally called normal concave plain, the tablet in Fig.7(d) shows a circular tablet generally called deep concave plain, tablet in Fig.7(e) shows a circular tablet generally called ball or pill, tablet in Fig.7(f) shows a circular tablet generally called flat beveled edge.

The tablet in Fig.8(a) shows a circular tablet generally called double radius, the tablet in Fig.8(b) shows a circular tablet generally called bevel and concave, the tablet in Fig.8(c) shows a circular tablet generally called dimple, the tablet in Fig.8(d) shows a circular tablet called ring, the tablet in Fig.8(e) shows a a circular tablet generally called rim, and the tablet in Fig.8(f) shows a capsule type tablet generally called capsule.

The tablet in Fig.9(a) shows an oval tablet generally called oval, the tablet in Fig.9(b) shows an elliptical tablet generally called ellipse, the tablet in Fig.9(c) shows a rectangular tablet generally called square, the tablet in Fig.9(d) shows a triangular tablet generally called triangle, the tablet in Fig.9(e) shows a pentangular tablet generally called pentagon, and the tablet in Fig.9(f) shows a hexagonal tablet generally called hexagon.

The tablet in Fig.10(a) shows a heptagonal tablet generally called heptagon, the tablet in Fig.10(b) shows an octagonal tablet generally called octagon, the tablet in Fig.10(c) shows a diamond-shaped tablet generally called diamond, the tablet in Fig.10(d) shows a pillow-shaped tablet generally called pillow or ballel, the tablet in Fig.10(e) shows a rectangular tablet generally called rectangle, and the tablet in Fig.10f) shows an almond-shaped tablet generally called almond.

The tablet in Fig.11(a) shows a sagittal tablet generally called arrow head, the tablet in Fig.11(b) shows a bullet-shaped tablet generally called bullet, the tablet in Fig.11(c) shows a semilunar tablet generally called half moon, the tablet shown in Fig.11(d) shows a shell-shaped tablet generally called shelled, the tablet in Fig.11(e) shows a heart-shaped tablet generally called heart, and the tablet in Fig.11(f) shows a star-shaped tablet generally called star.

(Comparison 3)

Magnesium stearate was added as lubricant for the granule produced like the experiment 2 in a ratio of 1.0 weight % for the entire amount of a tablet. After they were well mixed by a V type mixer, they were continuously tabletted by means of the punches 3, 4 and the die 1 used in the experiment 1 according to an internal lubricant method at a speed of rotating the rotary table at 30 times per minute.

WSG-type 15 by Glatt Co., Ltd. was used as a fluid-bed granulator and HATA HT-X20 by Hata Seisakusho Co., Ltd. was used as a main body of a tabletting machine.

For each experiment 2 and comparison 3, material was continuously tabletted for 5 hours by means of punches and a die constructing a female mold shown in Fig. 7 Fig.11 and produced tablet was sampled with time. Time which didn't cause sticking was measured by smoothness of produced tablet surface. In the experiment 2, sticking wasn't happened after 5 hours. However, in the comparison 3 sticking was happened after 1 hour and inferior goods were produced.

From the above-mentioned results, it became apparent that the tablet production method of the present invention could be preferably used for producing a tablet with an engraved mark or a dividing line, or an anomalous tablet.

The same experiments as the experiment 2 and the comparison 3 were executed for a tablet with an engraved mark or a dividing line. The punches 3, 4 and the die 1 of the external lubricant

spraying type tabletting machine A were housed in the spraying chamber 8, pulsating vibration air shown in Fig.4(a) was generated, magnesium stearate was applied as lubricant L on the surface 3s, 4s of the punches 3, 4 and the surface 1s of the die 1, and granule was continuously tabletted by means of the lubricated punches 3, 4 and the die 1. It was found that sticking was hardly caused for the tablet with an engraved mark or a dividing line in this case comparing with an internal lubricant method wherein material mixed with magnesium stearate as lubricant L was continuously tabletted.

(Embodiment of the Invention 3)

Here an example for producing a tablet (multiple unit tablet) including granule containing active substance (so called microcapsule) by means of the rotary type tabletting machine A shown in the embodiment of the invention 1 will be explained.

(Production of Granule on which Surface is Film Coated)

1) Reference 1 (production of sustained release microcapsule granule containing theophylline as active substance)

While a mixture of 50g of theophyline, 25g of cornstarch, 25g of powder sugar was added to 900g of circular granule crystalline cellulose (brand name : CELFIA, Asahi Chemical Industry Co., Ltd.) as nuclear particle by a quantitative feeder at a rate of 10g/min mass flow rate, 100g of ethanol losution in which 5g of hydroxypropylcellulose (brand name : HPC-L, Nippon

Soda Co., Ltd.) was dissolved was sprayed at a rate of 5g/min. mass flow rate , and the mixture was kneaded and granulated, using a centrifugal fluid coating means (CF-360 type, Freund Industrial Co., Ltd.). Then granule was taken out, left at rest for drying at 60℃ for one hour, and uncoated granule was obtained.

1.0kg of the obtained uncoated granule was fed in the centrifugal fluid coating means, 2000g of ethanol solution in which 100g of aminoalkylmetaacrilatecopolymer (brand name : EudragitRS, Röhm Pharma Co., Ltd.) was dissolved was spray coated, dried through circulation at 60℃ for twelve hours, then sustained release microcapsule granule was obtained (such obtained sustained release microcapsule granule is called reference 1).

2) Reference 2 (production of microcapsule formed with enteric coating)

1.0kg of the uncoated granule obtained in the reference 1 was fed in the centrifugal fluid coating means (CF-360 type, Freund Industrial Co., Ltd.), 1500ml of water dispersions comprising 180g of aminoalkylmetaacrilatecopolymer (brand name : EudragitRS, Röhm Pharma Co., Ltd), 18g of triacetin (Yuki Gosei Kogyo Co., Ltd.), 90g of talc as a dry solid standard was sprayed on 300g of 50 mesh lactose (brand name : DMV-50M, Pharmatose Co., Ltd.) at a rate of 6ml per minute, after the film was produced 60%, dried through circulation at 60℃ for

twelve hours, then enteric coating microcapsule was obtained (such obtained enteric coating microcapsule granule is called reference 2).

(Experiment 3)

700g of lactose for direct tabletting (brand name : tabletose, Taiyo Kagaku Co., Ltd.) and 300g of crystalline cellulose (brand name : AvicelPH101, Asahi Chemical Industry Co., Ltd.) were mixed with 1kg of the sustained release microcapsule granule of the reference 1 and granule for tabletting was obtained.

Magnesium stearate (Sakai Chemical Industry Co., Ltd.) was uniformly sprayed as lubricant L as dry type on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (lower surface) 4s of the lower punch 4 while pulsating vibration air is generated in the spraying chamber 8. The granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line. Then sustained release microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

The amount of magnesium stearate contained in the obtained sustained release microcapsule tablet (multiple unit tablet) was measured. It was 0.07 weight %.

In this experiment, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure,

and its peak was almost equal to or a litter lower than atmospheric pressure was used in this experiment.

(Experiment 4)

350g of lactose for direct tabletting and 150g of crystalline cellulose were mixed with 500g of enteric microcapsule of the reference 2 and granule for tabletting was obtained.

Magnesium stearate (Sakai Chemical Industry Co., Ltd.) was uniformly sprayed as lubricant L as dry type on the surface (inner wall) 1s of the die 1, the surface (lower surface) 3s of the upper punch 3, and the surface (lower surface) 4s of the lower punch 4 while pulsating vibration air is generated in the spraying chamber 8. The granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line as the punch 3 of the rotary type tabletting machine A shown in the embodiment of the invention 1. Then enteric microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

In this experiment, pulsating vibration air of which period was more than or equal to 1Hz and less than or equal to 10Hz, its valley was about 10% - 5% lower than atmospheric pressure, and its peak was almost equal to or a litter lower than atmospheric pressure was used in this experiment.

The comparisons 4 and 5 show examples when sustained release microcapsule tablet (multiple unit tablet) with a dividing line is produced according to the prior internal lubricant method.

(Comparison 4)

700g of lactose for direct tabletting, 280g of crystalline cellulose, and 20g of magnesium stearate as lubricant were mixed with 1kg of sustained release microcapsule granule of the reference 1 and granule for tabletting was obtained.

Then the granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line and sustained release microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

(Comparison 5)

700g of lactose for direct tabletting, 280g of crystalline cellulose, and 20g of magnesium stearate as lubricant were mixed with 1kg of enteric microcapsule granule of the reference 2 and granule for tabletting was obtained.

Then the granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line and enteric microcapsule tablet (multiple unit tablet) with a dividing line was obtained.

(Comparison 6)

In this comparison, sustained release microcapsule tablet (single unit tablet) was produced according to the prior internal lubricant method.

25g of theophylline, 700g of lactose for direct tabletting, 265g of crystalline cellulose, and 10g of magnesium stearate

as lubricant were mixed and granule for tabletting was obtained.

Then the granule was tabletted at a tabletting pressure of 500kg/punch, 1000kg/punch, and 1500kg/punch by means of a flat punch with a dividing line and uncoated tablet with a dividing line was obtained.

Then 2000g of ethanol dispersing liquid in which 100g of ethyl cellulose (brand name : ETHOCEL, DowChem. Co., Ltd.) was dispersed was sprayed to the obtained uncoated tablet and sustained release single unit tablet with a dividing line was obtained.

Next, relationship of tabletting pressure and hardness of tablet was examined for each experiment 3, 4, and comparison 4, 5.

(relation of tabletting pressure and hardness of tablet)

Mechanical strength (hardness) of the tablet obtained in the experiment 3, 4 and comparison 4, 5 was measured by means of tablet hardness measurement means (name : TH203CP, Toyama Sangyo Co., Ltd.).

The result is shown in table 3 and Fig.12.

Table 3

tabletting pressure (kg/punch)	Hardness			
	Experiment 3	Experiment 4	Comparison 4	Comparison 5
500	5.0	5.5	2.0	2.0
1000	10.0	11.0	4.5	5.0
1500	14.0	15.0	9.0	9.5

According to the result of the table 3 and Fig.12, a tabletting pressure over 1000kg/punch was required to obtain practical hardness (generally hardness to be destroyed at 3.7kg - 7.0kg is required) in the comparisons 4 and 5. However, it was found that adequate hardness was obtained at a tabletting pressure of 500kg/punch in the experiments 3 and 4.

From these results, it became clear that tablet with practical hardness could be produced at lower tabletting pressure than the prior art according to the present invention.

(Dissolution Test)

The tablet produced at a tabletting pressure of 500kg/punch in the experiments 3 and 4 (hereinafter called experiment 5 and experiment 6 respectively) and the tablet produced at a tabletting pressure of 1000kg/punch in the comparisons 4 and 5 (hereinafter called comparison 7 and comparison 8 respectively) were used as specimen of dissolution test.

In the dissolution test, dissolution rate was measured by a first liquid by Japanese Pharmacopoeia the 11th edition for first two hours, the specimen was pulled up after two hours

and transferred to a second liquid to obtain dissolution rate again according to a rotary basket method described in dissolution test of Japanese Pharmacopoeia the 11th edition.

The result is shown in the following table 4 and Fig.13.

Table 4

Dissolution Time (hour)	Experiment 5	Comparison 7	Reference 1	Experiment 6	Comparison 8	Reference 2
0	0	0	0	0	0	0
0.25	5	15	5	0	30	0
0.50	12	40	10	0	70	0
0.75	15	65	15	0	95	0
1.00	22	80	20	0	100	0
1.50	30	95	30	0	100	0
2.00	41	100	40	2	100	1
2.50	51	100	50	55	100	60
3.00	61	100	60	100	100	100
4.00	82	100	80	100	100	100
5.00	100	100	100	100	100	100

From the above-mentioned results of table 4 and Fig.13, it was found that each tablet in the experiment 5 and the experiments 6 showed similar dissolution behavior as the sustained release microcapsule granule (reference 1) and the enteric microcapsule granule (reference 2) respectively. According to the above-mentioned relation of the tabletting pressure and the tablet hardness, and the result of this experiment, it became apparent6 that the film coated on the surface of the microcapsule granule didn't cause damage while

tabletting because it could be tabletted at low pressure. On the other hand, it was found that each tablet in the comparisons 7 and 8 lost sustained release function and enteric function respectively.

(Dissolution Test of Dividable Tablet)

Next, equally divided tablet of the experiments 5 and 6 and equally divided tablet of the comparison 6 were used as specimen of dissolution test and dissolution rate was obtained according to the same method of the above-mentioned dissolution test.

The result is shown in the following table 5 and Fig.14.

Table 5

Dissolution Time (hour)	Experiment 5	Experiment 5 (divided)	Experiment 6	Experiment 6 (divided)	Comparison 6	comparison 6 (divided)
0	0	0	0	0	0	0
0.25	5	7	0	0	5	40
0.50	12	13	0	0	10	75
0.75	15	16	0	0	15	90
1.00	22	23	0	0	20	100
1.50	30	41	0	1	30	100
2.00	41	52	2	3	40	100
2.50	51	64	55	60	50	100
3.00	61	83	100	100	60	100
4.00	82	100	100	100	80	100
5.00	100	100	100	100	100	100

From the above-mentioned results of table 5 and Fig.14, it was found that the tablets in the experiment 5 and the

experiments 6 showed similar dissolution behavior as the sustained release microcapsule granule (reference 1) and the enteric microcapsule granule (reference 2) respectively and showed sustained release function and enteric function even if they were divided. However, the tablet in the comparison 6 lost sustained release function and enteric function when divided.

From the above results, it became apparent that the tablet (multiple unit tablet) in the present invention didn't lost sustained release function and enteric function even if they were divided.

In the embodiment of the invention 3 the multiple unit tablet of which granule surface was film coated was used. However, it is only an example. As a tablet having practical hardness can be produced at a low tabletting pressure according to the tablet production method of the present invention, a multiple unit tablet including active substance in a base matrix can be produced without destroying or plastically deforming the granule contained in the tablet.

When the amount of lubricant sprayed in the spraying chamber 8 is remarkably reduced like the embodiment of the invention 1, a tablet which doesn't contain lubricant therein and is provided with a minute amount of lubricant thereon can be produced, so that disintegration time of the tablet doesn't delay. Therefore, if the tablet is used as an uncoated tablet, it becomes

a rapidly disintegrable tablet and it is suitable as a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet. Further, if a film which can be dissolved at an objective region is coated on the surface, the tablet can be dissolved at the objective region when the film coat is dissolved. Accordingly, it is suitably used as a tablet which is required to be dissolved at the objective region.

The inventors of the present invention measured the disintegration time of the tablet and the dissolution time of active substance produced in the experiments 1 - 4. They found that the standard deviation thereof was within 10% of the average disintegration time of the tablet and the average dissolution time of active substance.

This embodiment showed an example in which a centrifugal fluid coating machine was used to produce granule to be contained in the tablet. However, warm air which is strengthened or weakened at a prescribed period may generated in a warm air conduit at a procedure of pelletizing the granule with a desired particle size, the granule may be pelletized in such a manner that a part of powder to be granulated and material under granulated always falls to be piled on a screen while pelletizing, and a film may be formed on the granulated material by spraying coating liquid on the granulated material. It is because that when material is granulated while warm air which is strengthened

or weakened at a prescribed period may generated in the warm air conduit at a procedure of pelletizing the granule with a desired particle size, the granule may be pelletized in such a manner that a part of powder to be granulated and material under granulated always falls to be piled on a screen while pelletizing, granulated material with small specific volume can be produced comparing with the granulated material which is produced by fluidizing powder to be granulated and material under granulated by means of steady flow warm air. The granulated material becomes hard so as to be scarcely damaged at the time of tabletting, therefore, a film coated on the granulated material becomes hardly damaged.

The process for coating a film on the granulated material isn't limited to the above-mentioned fluid-bed coating method. It may be executed according to a Pan coating method or a compression coating method.

Examples of using a rotary type tabletting machine are explained in the embodiments of the invention 1 - 3, however, they are only examples and the present invention can be executed by using a single-shot tabletting machine such as an eccentric type tabletting machine other than the rotary type tabletting machine.

In the above mentioned embodiments of the invention, a system wherein a hopper 15 is connected in midstream of the conduit 13 and the compression air generation means 16 such as an air

cylinder charged with compressed air is connected to the hopper 15 is explained. However, a system for discharging lubricant L stored in the hopper 15 isn't limited to such a system.

Fig.15 schematically shows a construction of such a system.

According to this system, a pulsating vibration air generation means 7A is connected to one end 13a of the conduit 13, a discharge port 15a of the hopper 15 is connected in midway of the conduit 13, and an elastic membrane 18 having an aperture (a slit in this example) 18a is provided for the discharge port 15a so as to become a bottom of the hopper 15 (see Fig.16).

The elastic membrane 18 is made of rubber such as a silicon rubber.

The member shown as 15b in Fig.15 is a lid and is provided for the hopper 15 removably and airtightly.

Next, operations of the system will be explained.

Fig.17 is an explanatory figure schematically showing operation of the system.

For using the system, the lid 15b is airtightly attached on the hopper 15 after lubricant L is contained in the hopper 15.

Then, when the pulsating vibration air generation means 7A is driven to supply positive pulsating vibration air to the conduit 13, the air pressure in the conduit 13 becomes higher than that in the hopper 15 while positive pulsating vibration air is at peak side. As shown in Fig.17(a), the elastic membrane

18 is deformed with its center curved upwardly in such a manner that the center becomes an antinode and the circumferential edge becomes a node.

In this case, the section of the aperture (slit in this example) 18a becomes V-shaped with its upper end opened. A part of lubricant L stored in the hopper 15 drops in the V-shaped aperture (slit in this example) 18a.

As positive pulsating vibration air changes from peak to valley, the air pressure in the conduit 13 is generally lowered so as to be the same as that in the hopper 15. The elastic membrane 18 is going to get back to its original shape because of its resilience as shown in Fig.17(b). The lubricant L dropped in the V-shaped aperture (slit in this example) 18a is caught in the aperture 18a.

When the positive pulsating vibration air supplied in the conduit 13 is at its valley, the air pressure in the conduit 13 becomes lower than that in the hopper 15 and the elastic membrane 18 is deformed with its center curved downwardly in such a manner that the center is antinode and the circumferential edge is node as shown in Fgi.17(c).

In this case, the section of the aperture (slit in this example) 18a becomes reverse V-shaped with its lower end opened. The lubricant L caught in the aperture 18a is discharged to the conduit 13.

Then the lubricant L discharged in the conduit 13 is

immediately mixed with positive pulsating vibration air supplied in the conduit 13 to be dispersed therein and is pneumatically transported to a spraying chamber (refer to the spraying chamber 8 in Fig.5).

The elastic membrane 18 repeats up and down vibration as shown in Fig.17(a) - Fig.17(c) according to vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air.

Therefore, as long as vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air supplied in the conduit 13 are fixed, the elastic membrane 18 vibrates up and down at a fixed vibration amplitude and frequency. Accordingly the amount of lubricant L discharged in the conduit 13 via the aperture (slit in this sample) 18a is constant.

Further according to this system, because positive pulsating vibration air is supplied in the conduit 13, there are no phenomenon such as adhesion of powdered material on the inner wall of the conduit 13 and blowing-out of powdered material in the conduit 13 which have been seen in the case that steady air pressure is used for pneumatically transporting powdered material.

Therefore, according to this system, lubricant L is discharged from the other end 13b of the conduit 13 at the same density as the lubricant L discharged to the conduit 13.

In other words this system can be functioned as a metering feeder.

Therefore, when the other end 13b of the conduit 13 is connected to the spraying chamber (refer to spraying chamber 8 in Fig.5), as long as the size of the aperture (slit in this example) 18a is fixed, and vibration amplitude, wave length, wave shape, and vibration frequency of positive pulsating vibration air supplied in the conduit 13 are fixed, lubricant L with constant density can be always supplied in the spraying chamber (refer to spraying chamber 8 in Fig.5).

Further, a media for pneumatically transporting lubricant L is air even if it is a positive pulsating vibration air so that the amount of lubricant L mixed with positive pulsating vibration air can be extremely minimized.

Accordingly, because a minute amount of lubricant L can be always sprayed in stable condition in the spraying chamber (refer to spraying chamber 8 in Fig.5), minute amount of lubricant L can be applied on the surfaces of the punches (the surface (lower surface) 3s of the upper punch and the surface (upper surface) 4s of the lower punch 4 as shown in Fig.2) and the surface (inner wall) 1s of the die 1.

In Fig.16, the elastic membrane has a slit 18a, however, this is only a preferable example. The aperture provided for the elastic membrane isn't limited to the slit 18a and the aperture may be small ones or the number isn't limited to one.

For example, an elastic membrane with plural small apertures 18b may be used as shown in Fig.18.

When the size and the number of the aperture or conditions (vibration amplitude, wave length, wave shape, and vibration frequency) of positive pulsating vibration air supplied in the conduit 13 are varied, the density of lubricant L supplied in the spraying chamber (refer to the spraying chamber 8 in Fig.5) can be changed diversely.

In this embodiment, a rotary type pulsating vibration air generation means 7A shown in Fig.3(b) and Fig.5(b) wherein the valve element 73 is provided rotatably around the rotary axis 74 so as to divide inside of the tube 72 into two parts is explained as a pulsating vibration air generation means. However, it isn't limited to such means 7A.

Fig.19 shows a section of other embodiment of pulsating vibration air generation means.

The high pressure pulsating vibration air generation means 7B is provided with a valve chamber 94 having a valve seat 9. between an input port 91 and an output port 92 and a valve plug 96 which is opened and closed by a cam mechanism 95.

The cam mechanism 95 is provided with a rotary cam 97 rotatable by a driving means such as a motor (not shown) and a roller 98 attached at the lower end of the valve plug 96.

The valve seat 93 is formed with a hole narrowing into the output port 92 and the valve plug 96 is formed like a reverse

mortar so as to conform to the shape of the valve seat 93 and designed to airtightly close the valve seat 93.

Further in this embodiment, an axis 96a of the valve plug 96 is provided in an axis hole 99h of a case 99 so as not to leak air and so as to be movably up and down.

The roller 98 is rotatably pinched by the rotary cam 97 and moves up and down according to a concavo-convex pattern on the rotary cam 97 while rotating.

More detailed, the rotary cam 97 is provided with an inner rotary cam 97a and an outside rotary cam 97b.

Concavo-convex pattern is provided for the inner rotary cam 97a and the outside rotary cam 97b respectively so as to keep distance of the roller 98 and to keep in line each other.

The roller 98 is pinched between the inner rotary cam 97a and the outside rotary cam 97b and is moved up and down while rotating according to the concavo-convex pattern provided for the inner rotary cam 97a and the outside rotary cam 97b by rotating the rotary cam 97 without causing jumping of the valve plug 96.

The convavo-convex pattern provided for the rotary cam 97 is selected according to physical property of lubricant L stored in the hopper 15.

In this embodiment, a flow rate control means 102 is provided for the input port 91 and compressed air which is generated by an air source 71 and of which flow rate is adjusted properly

by the flow rate control means 102 is supplied in the input port 91.

Further, one end of a conduit (the conduit 13 shown in Fig.3 or Fig.5) is connected to the output port 92.

The numeral 100 in Fig.19 shows a flow rate control port provided if required. An output control valve 101 for adjusting pressure of pulsating vibration air generated from the output port 92 is provided so as to be adjustable at a desired condition from full communication to atmospheric air and shut down from atmospheric air.

Next, operational procedure for generating positive pulsating vibration air having a desired period, vibration amplitude, and wave shape by means of the high pressure pulsating vibration air generation means 7B will be explained.

The rotary cam 97 which is easy to mix lubricant L with air according to physical property of lubricant L stored in the hopper 15 is attached to a rotary axis Ma of a driving means (not shown) of the high pressure pulsating vibration air generation means 7B.

Then the air source 71 is driven and a fixed amount of compressed air is supplied to the input port 92 by adjusting the flow rate control means 102.

Further, the rotary cam 97 is rotated at a fixed rotational velocity by actuating the driving means (not shown).

The pressure of pulsating vibration air discharged from

the output port 92 is controlled by adjusting the output control valve 101, if required.

When the rotary cam 97 is rotated at a fixed rotational velocity, the valve plug 96 moves up and down according to the concavo-convex pattern of the rotary cam 97. Therefore, when the valve seat 93 is controlled at full closed, half opened, or full opened according to the concavo-convex pattern of the rotary cam 97, pulsating vibration air with a desired wave shape can be outputted from the output port 92.

According to the high pressure pulsating vibration air generation means 7B, rotational velocity of the rotary cam 97 may be changed by controlling the driving means (not shown) in order to obtain a desired period of pulsating vibration air discharged from the output port 92. Further, the air source 71, the flow rate control means 102, and/or the output control valve 101 may be appropriately controlled in order to obtain a desired vibration amplitude of pulsating vibration air discharged from the output port 92.

Industrial Applicability

As mentioned above, according to the tablet production method in claim 1, lubricant is sprayed at the same time pulsating vibration air is generated in the spraying chamber. When lubricant is sprayed in the spraying chamber while pulsating vibration air is generated, lubricant is mixed with pulsating

vibration air.

Further according to this method, lubricant is applied on the surfaces of a pair of punches and a die while lubricant is mixed with pulsating vibration air, namely under difficult condition to apply lubricant on the surfaces thereof.

When lubricant is going to be applied on the surfaces under such a difficult condition, it can be uniformly applied on the surfaces of the pair of punches and the die.

Accordingly, as molding material is hardly adhered on the pair of punches and the die, sticking and so on aren't apt to be caused on the produced tablet in this tablet production method.

Moreover, as the result that lubricant is uniformly applied on the surfaces of the pair of punches and the die, the produced tablet hardly causes sticking and so on comparing with the prior internal lubricant method and the prior external lubricant spraying method eve if the amount of lubricant used for a tablet is remarkably reduced.

Herewith, as a tablet on which surface minute amount of lubricant is attached can be produced, the tablet produced by this method doesn't happen disintegration time delay because of water repellency of lubricant.

Therefore according to this tablet production method, a tablet which can be disintegrated at an objective region such as target region of living body can be produced.

Moreover according to the method, because molding material

doesn't include lubricant therein, a tablet having practical hardness can be produced even if its tabletting pressure is lower than that of prior art when molding material is tabletted with the die and the pair of punches.

Hence, when a tablet including granule on which surface a film is coated is produced, the film formed on the surface of the granule isn't destroyed.

And when a tablet including granule containing active substance in the base matrix is produced, the function of the matrix contained in the tablet isn't damaged.

According to the tablet production method in claim 2, lubricant mixed with pulsating vibration air is designed to be sprayed in the spraying chamber.

Further according to this method, lubricant is applied on the surfaces of a pair of punches and a die while lubricant is mixed with pulsating vibration air, namely under difficult condition to apply lubricant on the surfaces thereof.

When lubricant is going to be applied on the surfaces under such a difficult condition, it can be uniformly applied on the surfaces.

Accordingly, as molding material is hardly adhered on the pair of punches and the die, sticking and so on aren't apt to be caused on the produced tablet in this tablet production method.

Moreover, as the result that lubricant is uniformly applied on the surfaces of the pair of punches and the die, the produced

tablet hardly causes sticking and so on comparing with the prior internal lubricant method and the prior external lubricant spraying method eve if the amount of lubricant used for a tablet is remarkably reduced.

Herewith, as a tablet on which surface minute amount of lubricant is attached can be produced, the tablet produced by this method doesn't happen disintegration time delay because of water repellency of lubricant.

Therefore according to this tablet production method, a tablet which can be rapidly disintegrated at an objective region such as target region of living body can be produced.

Moreover according to the method, because molding material doesn't include lubricant therein, a tablet having practical hardness can be produced even if its tabletting pressure is lower than that of prior art when molding material is tabletted with the die and the pair of punches.

Hence, when a tablet including granule on which surface a film is coated is produced, the film formed on the surface of the granule isn't destroyed.

And when a tablet including granule containing active substance in a base matrix is produced, the function of the matrix contained in the tablet isn't damaged.

According to the tablet production method in claim 3, a spraying means for spraying lubricant mixed with positive pulsating vibration air is provided in the spraying chamber,

so the production system can be simplified.

According to this method, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film and the base matrix aren't devised for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste.

According to the tablet production method in claim 5, a tablet with practical hardness can be produced at low tabletting pressure because lubricant isn't included in molding material. Therefore, a tablet can be produced without breaking film and granule and without causing plastic deformation even if the construction and material of the film and the base matrix aren't devised for the purpose of prolongation of mode of action, sustained release, rapid release, high solubility in stomach, high solubility in intestine, prevention of bitter taste.

According to the tablet production method in claim 6, a spraying means for spraying lubricant mixed with positive pulsating vibration air is required to be provided so that the system can be simplified.

According to the tablet production method in claim 7, granule containing active substance and diluting agent is used as granule

containing active substance (so called microcapsule) so that the particle diameter and particle size containing active substance can be easily changed.

Therefore, a tablet can be easily produced by controlling the diameter and the size of granule containing active substance so as to facilitate coating on the surface.

Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

According to the production method in claim 8, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the function of a base matrix even if granule contained in the tablet includes active substance in the base matrix.

According to the production method in claim 9, because tablet can be produced at low tabletting pressure, a tabletting can be executed without destroying the coating film even if granule contained in the tablet is coated with a film.

According to the tablet production method in claim 10, tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the dies so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

According to the tablet production method in claim 11,

tabletting is continuously executed utilizing the fact that molding material isn't adhered on the punches and the dies so that sticking isn't caused. A tablet including active substance and a tablet including granule containing active substance can be produced at industrial production base.

According to the tablet production method in claim 12, because lubricant is applied on the surface of the punches and the dies constructing a female mold for a tablet with an engraved mark or a dividing line and for an anomalous tablet in the spraying chamber in which pulsating vibration air is generated, lubricant can be applied uniformly comparing with the prior external lubricant spraying method. As a result, molding material is hardly attached on the surfaces of the punches and the dies while compressing a tablet with an engraved mark or a dividing line or an anomalous tablet so that sticking, capping, and laminating of such a tablet are prevented.

According to the tablet production method in claim 13, as tabletting pressure for compressing molding material is low, tabletting can be executed without destroying a film even if granule contained in the tablet is covered with a film. Further, if granule contained in a tablet includes active substance in a base matrix, tabletting can be executed without destroying the function of the base matrix.

According to the tablet production method in claim 14, even if the amount of lubricant sprayed at one tabletting is

remarkably reduced, a tablet can be produced without causing sticking and so on. Consequently the produced tablet doesn't include lubricant therein and minute amount of lubricant is attached on the surface so that disintegration time isn't delayed.

Further according to this method, tablet can be produced at a low tabletting pressure, and the granule is hardly destroyed or plastic deformation is caused, so that the function of the granule containing active substance in the tablet isn't apt to be damaged.

Therefore, according to the production method, if the produced tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and a tablet which is required to be immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet can be easily produced. Further if a film coat which can be dissolved at an objective region is executed on the surface of a tablet, the tablet itself is immediately dissolved at a desired region when a film coat is dissolved, so that a tablet which can be dissolved at an objective region can be produced.

According to the tablet in claim 15, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegrant time of the tablet delays because of water repellency of lubricant.

Therefore, if the tablet is used as an uncoated tablet,

it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and active substance contained in the tablet is immediately released.

Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at an objective region when the film coat is dissolved, so that active substance contained in the tablet is immediately released.

According to the tablet in claim 16, as lubricant isn't included therein and a minute amount is attached on the surface, there is no problem such that disintegrant time of the tablet delays because of water repellency of lubricant.

Therefore, if the tablet is used as an uncoated tablet, it becomes a rapidly disintegrable tablet and the tablet is immediately disintegrated at an objective region like an intrabuccally rapidly disintegrable tablet and granule containing active substance (so called microcapsule) contained in the tablet is immediately released.

Moreover, if a film coat which can be dissolved at an objective region is executed on the surface of the tablet, the tablet itself can be dissolved at an objective region when the film coat is dissolved, so that granule containing active substance (so called microcapsule) contained in the tablet is immediately released.

According to the tablet in claim 17, as granule containing active substance and diluting agent is used as granule containing active substance (so called microcapsule), the particle diameter and size of the granule can be easily modified by diluting agent.

Therefore, a tablet production can be easily executed by controlling the particle diameter and size of the granule containing active substance so as to coat a film on the surface of the tablet.

Further, the diameter and the size of granule containing active substance can be made so as to derive the function of granule to the full extent.

According to the tablet in claim 18, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

Further, as the tablet includes granule containing active substance in the base matrix, the base matrix can achieve its desired objective function.

For example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of sustained release by the base matrix.

Therefore, if unfilmed granule containing active substance and granule containing active substance in base matrix are mixed in a tablet, they are immediately released from the tablet when

the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

As for the granule containing active substance in the base matrix, for example, if the base matrix aims at prolongation of mode of action, the tablet also becomes to have a function of prolongation of mode of action by the base matrix.

Namely, the tablet has both rapid onset of action and prolongation of mode of action.

If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and granule containing such agent in the base matrix are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

According to the tablet in claim 19, as diluting agent used as bulking agent doesn't include lubricant, there is no problem such that disintegration time of the tablet delays because of water repellency of lubricant.

Further, as the tablet includes granule containing active substance, a film coated on the surface of the granule containing active substance brings out a desired objective function.

For example, the film coated on the granule containing active substance aims at prolongation of mode of action, the tablet also has prolongation of mode of action because of the film.

Therefore, if unfilmed granule containing active substance and filmed granule containing active substance are mixed in a tablet, they are immediately released from the tablet when the tablet is dissolved. The active substance contained in the unfilmed granule is immediately absorbed in a body when the tablet is disintegrated. Therefore, the tablet has superior rapid onset of action.

As for the filmed granule containing active substance, for example, if the film aims at prolongation of mode of action, the tablet also becomes to have prolongation of mode of action because of the function of the film.

Namely, the tablet has both rapid onset of action and prolongation of mode of action.

If the active substance is analgesic, anti-inflammatory agent, or antidote, unfilmed granule containing such agent and filmed granule containing such agent are mixed. Thereby, a new tablet such as a once daily tablet, namely a quick & slow release tablet, by which pain, inflammation or fever of a patient is immediately remedied and analgesic action, anti-inflammatory action, or antidote action is kept long when a patient takes this medicine can be obtained.

Because the tablet in claim 20 is provided with a minute

amount of lubricant on the surface, its disintegration time doesn't delay.

As the tablet in claim 21 has a dividing line, it can be easily divided along the line. Therefore, appropriate amount of drug depending on the weight or age of a patient can be taken by a patient.

Because the tablet in claim 22 has anomalous shape, drugs can be easily distinguished by its shape. Therefore, medication error is hardly happened.

According to the tablet in claim 23, because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance. Therefore, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than 15.0 percent of average disintegrating time or average elution time can be easily produced.

Further, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than 10.0 percent of average disintegrating time or average elution time, which has been considered to be difficult in the prior art, can be easily produced.

Moreover, the tablet of which standard deviation of disintegrating time of the tablet or elution time of the active substance is less than 7.5 percent of average disintegrating

time or average elution time, which has been impossible to produce in the prior art as far as the inventors know, can be produced.

Because lubricant is uniformly applied on the surface of the tablet (uncoated tablet), there is no wide variation of disintegration time of the tablet and elution time of the active substance.

Hence, there is no variation of the time before appearing the effect of drugs between tablets.

According to the tablet in claim 24, as magnesium stearate is used as lubricant, the amount of lubricant contained in the tablet can be easily measured.